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Running title

Cortisol predicts psychological therapy response

Cortisol as a predictor of psychological therapy response in depressive disorders – systematic review and meta-analysis

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2 Supplementary tables

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Abstract

Background

Many patients with depressive disorders demonstrate resistance to psychological therapy. A frequent finding is hypothalamic-pituitary-adrenal (HPA) axis alterations. As cortisol is known to modulate cognitive processes, those patients may be less likely to profit from psychological therapy.

Aims

To conduct a systematic review and meta-analysis on cortisol as a predictor of psychological therapy response.

Method

The Cochrane Library, EMBASE, MEDLINE, and PsycINFO databases were searched. Records were included if they looked at patients with any depressive disorder engaging in psychological therapy, with a pre-treatment cortisol and a post-treatment symptom measure.

Results

Eight articles satisfied our selection criteria. The higher the cortisol levels before starting psychological therapy, the more symptoms depressed patients experienced at the end of treatment and/or the smaller their symptom change.

Conclusions

Our findings suggest that depressed patients with elevated HPA functioning are less responsive to psychological therapy.

Declaration of interests

The authors declare no conflicts of interests.

Introduction

Psychological therapies are amongst the most effective treatments for depressive disorders, with most evidence focusing on cognitive-behavioural therapy (CBT; 1). However, around 50% of patients do not respond to psychotherapeutic interventions (1). Upon repeated non-response to a number of treatment modalities, those patients are sometimes referred to as “treatment-resistant” patients. The illness course of this subgroup is most often relapsing or chronic (2), high levels of disability and mortality are common (3), and these patients make up the largest proportion of direct (e.g., treatment) and indirect (e.g., lost productivity; 4, 5) costs. Amongst the most salient features of depressive disorders are alterations in the hypothalamic-pituitary-adrenal (HPA) axis, one of the major stress-responsive systems. Hypercortisolism, i.e., high circulating levels of cortisol, potentially due to impaired negative feedback sensitivity, is a common finding in depression (6, 7). It is noteworthy that cortisol modulates cognitive processes. In patients with major depression, cortisol seems to be related to cognitive impairment, and may thus explain symptoms such as concentration and memory difficulties (8). As a consequence, these patients may be less able to engage in learning processes, as occurring during psychological therapy. Based on these findings, it is conceivable that pre-treatment cortisol levels serve as a predictor of psychological therapy response in patients with depressive disorders. More specifically, we would hypothesise that patients demonstrating the most pronounced basal HPA axis alterations would be at risk of profiting less from the corrective learning experiences that are made during therapy. In the case of depression, this would mean that the higher a patient’s basal cortisol levels, the higher their level of depression would remain upon completing therapy. Similarly, the extent to which a patient shows HPA axis alterations following standardised neuroendocrine testing (stimulation or suppression tests), psychosocial stressors, or natural challenges such as awakening (“post-challenge cortisol”) would also likely be associated with poorer response. Our aim was to systematically review the literature on cortisol levels as a predictor of psychological therapy response and to quantify the strength of this relationship.

Method

Search strategy

Relevant records were identified by one of the study investigators (SF) by systematically searching the Cochrane Library, EMBASE, MEDLINE, and PsycINFO databases from the first available year until

March 2015. We combined key words and subject headings in accordance with the thesaurus of each database and applied exploded subject headings. Our search string consisted of three components: 1) “cortisol” and synonyms, 2) “depressive disorder”, including synonyms and related terms, and 3) “psychological therapy” and synonyms. All searches were restricted to studies conducted in humans. No language restrictions were applied.

Screening and selection procedure

Identified records were screened regarding the following inclusionary criteria: 1) children, adolescent or adult outpatients or inpatients primarily suffering from any depressive disorder (i.e., major depressive disorder, persistent depressive disorder, or adjustment disorder with depressed mood) diagnosed according to DSM or ICD criteria, 2) any kind of pre-treatment cortisol assessment, and 3) psychological therapy (i.e., any treatment including at least one session of behavioural therapy, cognitive therapy, CBT, interpersonal therapy, psychodynamic therapy, or psychoanalysis delivered by a trained clinician) including a standardised post-treatment symptom measure. Comorbidity with mental disorders was not exclusionary, and neither was comorbidity with medical diseases or previous or current intake of medication. Studies delivering a combination of psychological and pharmacotherapy were excluded. Full-text articles were retrieved and checked for relevant analyses. The reference sections of all articles were then searched for additional records.

Data extraction

For each identified study one of the study investigators (SF) collected information about the first author, its year of publication, number of treated patients, their sex and age, their primary diagnosis, eligibility criteria (e.g., comorbidity and medication), study design, type and intensity of psychological therapy, pre-treatment levels of cortisol in hair, urine, saliva, or blood, post-treatment symptom scores of depression, and adjustment for covariates. This information is reported in the online supplementary Table 1. When multiple cortisol measures were reported, we favoured hair, urinary and salivary cortisol over plasma cortisol. This was to obtain a measure of free (i.e., unbound cortisol, as found in these media) rather than total cortisol (9). Moreover, we were interested in obtaining stable measures, which is why long-term (e.g. 3 cm hair cortisol) or aggregate indices (e.g. areas under the curve) were preferred over single time point assessments. Evening or afternoon measurements were to be

extracted in preference to morning levels, as due to the diurnal rhythmicity of cortisol inter-individual variability is lower later in the day (9). When psychological therapy response was assessed at multiple time points, the assessment closest to the last therapy session was selected. Symptoms of depression were chosen as outcome variables. Whenever studies used multiple symptom measures as outcome variables (e.g., different questionnaires assessing depression), an average effect size was calculated and extracted. Risk of bias was assessed by means of an adapted version of a quality tool that was used in an earlier meta-analysis on the role of cortisol in functional somatic syndromes (10). We used eight of the original nine items (item two was excluded due to non-applicability) and scored them using the same three-point scale (0-2). An additional item regarding the duration (weeks) and frequency of psychological therapy (number of sessions) was added; if both were stated, the study obtained a score of 2, if duration or intensity was stated, it was given a score of 1, and a score of 0 was given to those not giving any information about either of these characteristics. The complete checklist can be found in the supplementary Table 2. The maximum attainable quality score was 18.

Effect size calculation

To quantify the relationship between cortisol levels at baseline and psychological therapy response, correlation coefficients (r) were directly extracted by one of the study investigators (SF) or, if not available, calculated based on summary statistics, such as frequency tables, means, standard deviations, and sample sizes, or t values and sample sizes. This was done in in accordance with the procedures outlined by Lipsey and Wilson (11). In brief, statistics are converted into target effect sizes (in this case r) by means of mathematical formulas. For instance, the standardised mean effect size d is calculated based on means, standard deviations, and sample sizes and d in turn is converted into r using $r = d/\sqrt{(d^2+a)}$, with a being a correction factor that is used in the case of unequal sample sizes, and $a = (n_1+n_2)^2/n_1n_2$ (12). Whenever correlation coefficients (r) were directly extracted, we used either correlations between cortisol values and symptoms of depression upon completion of treatment (controlled for pre-treatment levels of the same symptoms), or correlations between cortisol values and change in symptoms (delta values). We extracted data that were adjusted for relevant covariates rather than unadjusted data whenever possible. In cases where no or insufficient statistical parameters were reported regarding our research question, the authors were contacted. If we were unable to gather additional data from the authors and it was stated that no significant relationship

between pre-treatment cortisol levels and response to psychological therapy was found, we included a conservative effect size (ES) of 0 into our meta-analysis.

Statistical analysis

We calculated Fisher's Zr and 95% confidence intervals (CI) for each study and weighed studies based on their sample size (11). Studies with an extreme ES (below or above two standard deviations) were to be excluded. Separate analyses for basal cortisol and post-challenge measures were conducted. An aggregated ES including a 95% CI was calculated for each analysis, using SPSS 21 and the macros developed by David B. Wilson (http://mason.gmu.edu/~dwilsonb/ma.html). As significant statistical heterogeneity according to the Q and I^2 statistics was predicted in all analyses, random rather than fixed effects models were considered appropriate (13). Sensitivity analyses were applied for studies with unclear eligibility. Publication bias was planned to be examined by visual inspection of funnel plots. In addition, Egger's test (14) and a trim and fill procedure (15) were to be used for quantification of publication bias.

Results

Search results

Our search yielded 25,991 records, of which 84 were considered potentially relevant based on their title or abstract. Of these, 76 were excluded because they were not original research (e.g., reviews), not conducted in depressed patients, did not assess cortisol levels, did not include any treatment at all, administered drugs as part of the treatment package, used specific interventions that did not meet our definition of psychological therapy (e.g., aerobic exercise), were retrospective (e.g., compared cortisol levels of treatment-resistant patients to healthy controls), or did not report predictor analyses. In one study, patients and healthy controls or patients receiving different kinds of treatments had been collapsed for statistical analyses (16). As the data set of this study was not available, it was excluded. In one paper, the authors stated that no relationship between pre-treatment cortisol levels and psychological therapy response was found (17). As no standardised regression coefficients were available with this report, we imputed an ES of 0 (95% CI [-0.512, 0.512]). Two reports were likely to have patient overlap according to the authors (18, 19), but as this could not be quantified, both were included into the initial analyses and assessed in sensitivity analyses. Another sensitivity analysis was

conducted excluding the study that used clomipramine in a pharmacological challenge test of the HPA axis (all remaining studies used the dexamethasone challenge test). In total, eight studies were eligible for data extraction. Tables 1 (online supplement) shows the characteristics of these studies.

Systematic review and meta-analysis

Eight studies were included with a total of 212 cases. Two studies focused on adolescents (17, 20) and one looked at older adults (21). The majority of patients had a major depressive disorder according to the DSM, and in most instances, patients had moderate to severe depression. Patients with major comorbid mental disorders, including substance use, psychotic, and bipolar disorders, were mostly excluded. By contrast, patients with comorbid medical diseases were often still considered eligible, that is, if their illness was unlikely to affect their depression, HPA axis functioning, or treatment itself. The handling of psychotropic medication was rather heterogeneous across studies: intake of medication was excluded a priori, discontinued shortly before treatment, or kept stable over the course of treatment.

The distribution of outpatients to inpatients was 50:50. All patients received cognitive therapy or CBT, except for the two adolescents studies where patients were treated with interpersonal therapy (17, 20). Outpatients were treated on a weekly basis for a total duration of eight to 16 weeks. Inpatients had three to five sessions of psychological therapy per week, lasting between three and six weeks. Basal levels of cortisol were determined in urine, blood, or saliva. The earlier studies were primarily interested in post-challenge cortisol levels and used the dexamethasone suppression test to assess this. This test allows the assessment of negative feedback sensitivity by administering 1 mg of a synthetic analogue of cortisol; higher concentrations of cortisol on the day after dexamethasone administration indicate alterations (hyperactivity) in the HPA axis. Patients were often divided into non-responders and responders. One study challenged the HPA axis by administering the tricyclic antidepressant clomipramine, and here, lower cortisol concentrations were considered maladaptive (22). The Beck Depression Inventory and Hamilton Rating Scale for Depression were the most frequently employed therapy response measures. Again, some studies divided patients into groups of non-responders and responders.

Quality scores ranged from 7 to 13 out of a maximum of 18 points. The quality of the diagnostic assessment, stating of eligibility criteria, the description of psychological therapy and the statistical reporting were very satisfactory in general. On the other hand, virtually no information on the duration of patients' illness and on the blindness of therapists and assessors of treatment response to patients' cortisol levels was provided. The description of HPA axis assessment and the handling of confounders varied greatly.

Results were fairly consistent: Half of the studies found that patients with higher basal or post-challenge cortisol levels retained higher levels of depression upon completion of psychological therapy (18, 20, 23, 24). Two more studies were in line with these findings, although only with regard to some of the employed cortisol and depression measures (19, 21). More specifically, in the study by Thase et al., only basal levels of cortisol (but not post-challenge levels) were associated with treatment response, whereas basal cortisol levels in the study by Holland et al. only predicted change in depression levels when the three used outcome scales were combined to create a global depression index. Two studies did not find any association between cortisol levels and psychological therapy response (17, 22). Subsequent meta-analysis confirmed the overall finding: a significant relationship between basal cortisol levels (five independent ES, mean ES = 0.264, 95% CI [0.047, 0.481]; Z = 2.382, p = .017) and post-challenge cortisol levels (six independent ES, mean ES = 0.421, 95% CI [0.095, 0.748]; Z = 2.528, p = 0.012) and response to psychological therapy emerged, indicating that higher cortisol levels pre-treatment were associated with more severe symptoms post-treatment or smaller changes in symptoms (see Figures 1 and 2 for forest plots).

- Insert Figures 1 and 2 here -

Significant heterogeneity was present regarding post-challenge cortisol levels (Q = 15.22, p = 0.010, I^2 = 67.15%), but not regarding basal levels (Q = 5.55, p = .235; I^2 = 27.93%). However, due to the low number of included studies, the latter result cannot be regarded as definitive evidence for the absence of heterogeneity. For the same reason, Egger's test and the trim and fill procedure were not undertaken. Sensitivity analyses were conducted by repeating analyses without the study where an effect size had been imputed (17), without the study that was likely to have some degree of case overlap with a later report (18), and without the one using clomipramine to challenge the HPA axis

(22). Excluding the study that possibly overlapped with another included study rendered our previously significant association between basal cortisol levels and outcomes significant by trend only (four independent ES, mean ES = 0.215, 95% CI [-0.029, 0.460]; Z = 1.726, *p* = .084). However, the positive finding of post-challenge cortisol levels predicting treatment response remained significant and no other changes of our results occurred as a result of excluding the other two studies.

Discussion

The main finding of the present meta-analysis is that the higher the basal and post-challenge cortisol levels before starting psychological therapy, the more symptoms depressed patients experienced at the end of treatment and/or the smaller their symptom change.

This finding is in line with our initial hypothesis that HPA axis alterations, in this case indicated by high cortisol levels, are associated with worse psychological treatment outcomes in depressed patients. Importantly, basal levels of cortisol were associated with response to psychological therapy by trend only when one study was excluded that had potential patient overlap with another study. As it was not possible to determine whether this overlap actually occurred or not, this finding needs to be interpreted with caution. Cortisol in response to the dexamethasone suppression test, on the other hand, did predict treatment response in the present meta-analysis. This is interesting from a clinical point of view, as the dexamethasone test offers the possibility of assessing HPA axis integrity in a highly standardised manner. In addition, the dexamethasone depression test can now be undertaken using salivary cortisol measures making it a more practical test that can be undertaken at home without the need for venepuncture or hospital attendance (13). Importantly, however, our findings may not be applicable to patients with atypical depression, who have been found to present with low rather than high cortisol values (7).

One explanation for our findings is evidence that HPA axis alterations may be linked with cognitive functioning. According to this line of reasoning, the more pronounced a depressed patient's HPA axis alterations, the more severe his/her cognitive impairment, which in turn renders him/her less capable of engaging in psychological therapy. Based on our findings, it may be sensible to combine psychological therapy with psychotropic medication, which specifically targets hypercortisolism, such as antidepressants (25) or anti-glucocorticoid agents (e.g., mifepristone; 26). However, considering the low overall number of published studies, the possibility of publication bias, the age of certain

studies, and the heterogeneity detected, further research on cortisol as a predictor of psychological therapy responses is clearly warranted before treatment suggestions can be made based on the findings reported here.

Strong evidence suggests that HPA axis alterations in depression originate from experiences of childhood trauma and chronic stress (27, 28). Apart from direct effects on treatment efficacy via cognitive impairment, hypercortisolism may thus indicate a specific subgroup of patients with depression, and one that has its aetiology in earlier life trauma or chronic stress (29, 30). In fact, a recent meta-analysis showed that those depressed patients who reported childhood maltreatment had poorer responses across treatment modalities (31). Apart from the above-mentioned psychotropic agents, clinicians may therefore consider interventions that have a strong focus on trauma and/or interpersonal functioning, with the latter being an important source of chronic stress. Moreover, findings of a recent trial suggest that mindfulness-based cognitive therapy (MBCT) may be specifically useful for patients who report childhood trauma (32). Taken together, this line of evidence suggests it would be highly commendable for future studies on cortisol as a predictor of treatment response to stratify patients according to their levels of childhood trauma, and to test whether the findings we report here are driven by a specific subgroup of depressed patients.

Several limitations need to be considered when interpreting our results. First, our search yielded very few suitable studies. As a result of this, publication bias could not be assessed. Second, in some studies, important information was not reported, such as whether the assessors of treatment response were blind to the subjects' cortisol levels. Another point is that covariates (e.g., psychotropic medication, baseline levels of depression) influencing cortisol levels and/or its association with treatment response have not been consistently taken into account. Third, there was substantial heterogeneity in eligibility criteria, cortisol and treatment response assessment within the included studies. Unfortunately, the small number of studies prevented us from exploring which factors were most strongly related to positive findings.

Taken together, our findings suggest that pre-treatment cortisol concentrations may predict responses to psychological therapy in patients with depression. Accumulating evidence suggests that there may be a subtype of depression that has its origins in early life stress, which could take its toll on stress-responsive bodily systems, such as the HPA axis, and in turn mediate some aspects of the treatment resistance seen in these patients. Hypothalamic-pituitary-adrenal axis markers are thus a

promising avenue in research on treatment resistance. More studies that address the research question outlined in this meta-analysis are warranted. Future research may consider using long-term measures of HPA axis functioning, such as finger nail or hair cortisol concentrations, that most accurately represent the patients' pre-treatment state, controlling for confounding factors, in particular depression severity and childhood trauma, and using continuous response scores when evaluating treatment success.

Contributions

SF and AJC conceived and designed the study. SF analysed and interpreted the data and drafted the article. AJC, RS and AH interpreted the data and revised the article for important intellectual content. All authors approved the final version to be published.

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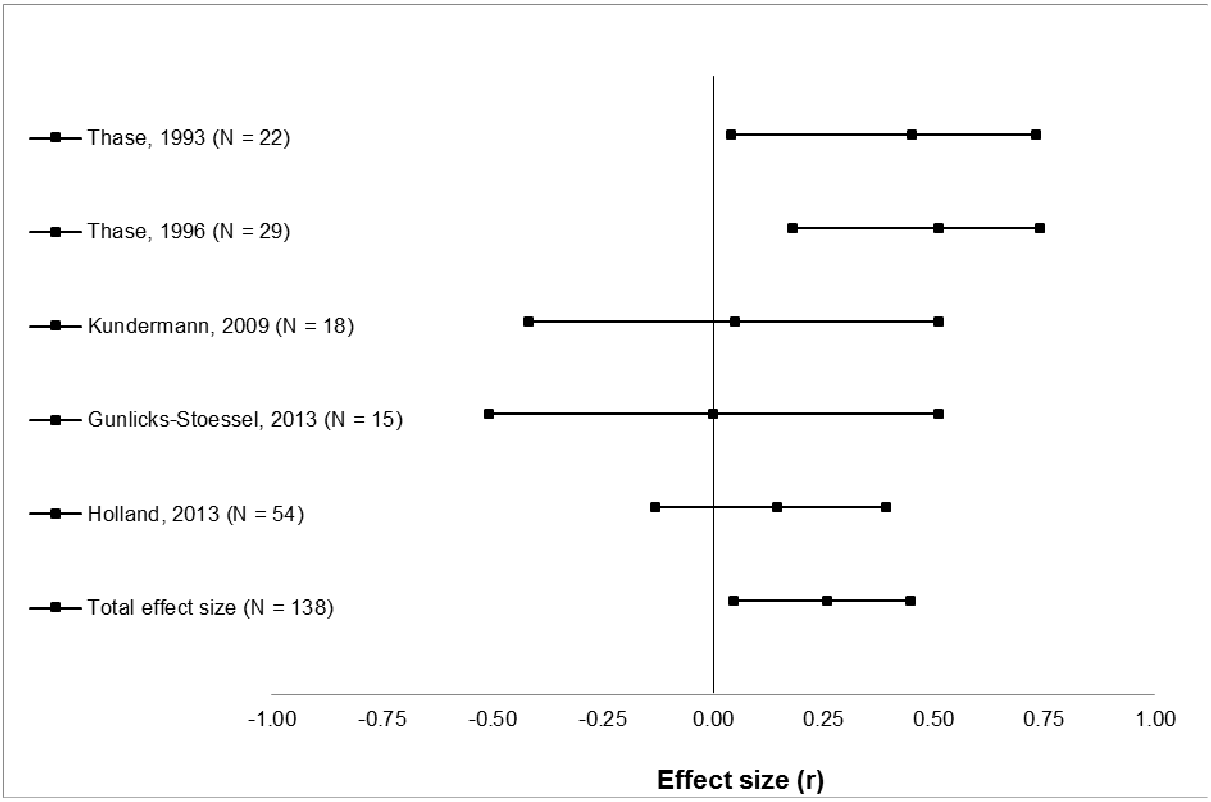

Figure 1 Forest plot regarding the association between basal cortisol levels pre-treatment and psychological therapy response in patients with depressive disorders. Positive correlation coefficients mean that high pre-treatment levels of cortisol were associated with either higher scores on measures of depression post-treatment or with lower change scores (in the latter case, coefficients were inverted for illustrative purposes). When multiple cortisol measures were reported, urinary and salivary cortisol were favoured over plasma cortisol, aggregate indices over single time point assessments, and evening or afternoon measurements over morning levels. When multiple depression measures were used as outcome variables, an average effect size was calculated and extracted. The plot shows the correlation coefficients and 95% confidence intervals for each included study.

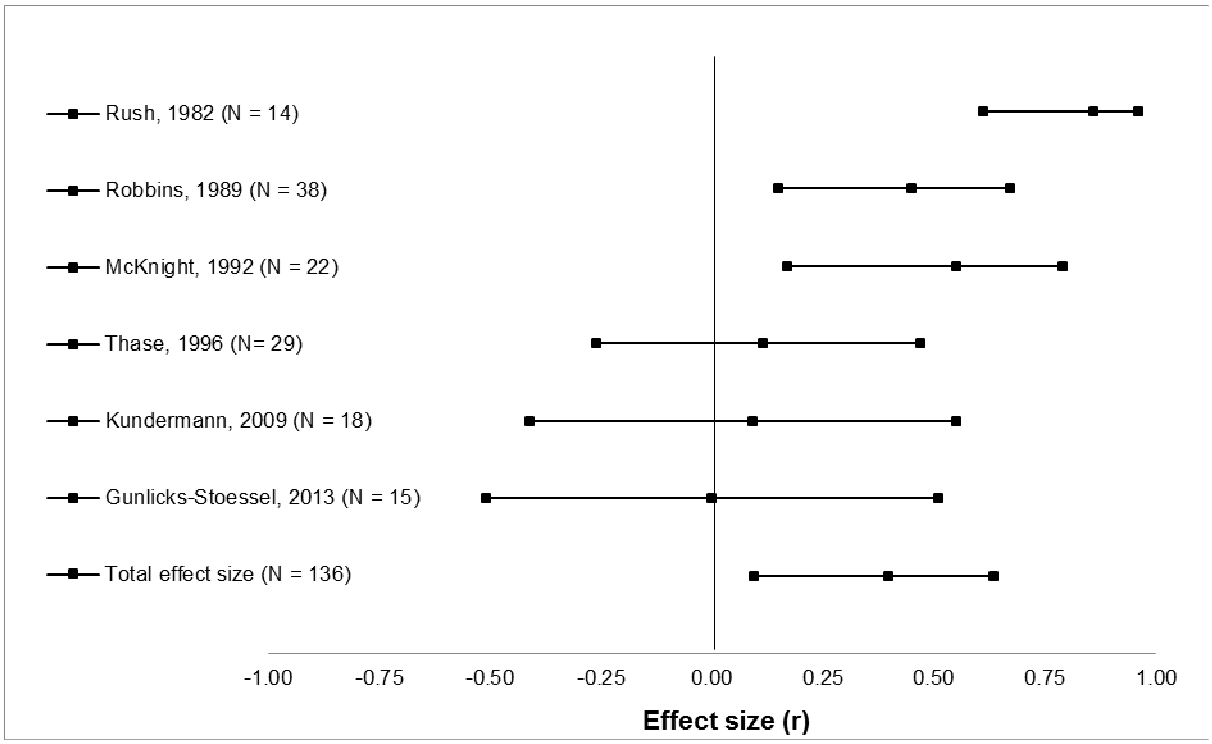

Figure 2 Forest plot regarding the association between post-challenge cortisol levels pre-treatment and psychological therapy response in patients with depressive disorders. Positive correlation coefficients mean that high pre-treatment levels of cortisol were associated with either higher scores on measures of depression post-treatment or with lower change scores (in the latter case, coefficients were inverted for illustrative purposes). When multiple cortisol measures were reported, urinary and salivary cortisol were favoured over plasma cortisol, aggregate indices over single time point assessments, and evening or afternoon measurements over morning levels. When multiple depression measures were used as outcome variables, an average effect size was calculated and extracted. The plot shows the correlation coefficients and 95% confidence intervals for each included study.

Table 1 Characteristics of included studies on cortisol as a predictor of psychological therapy response in patients with depressive disorders

Study	Sample	Setting and treatment	Cortisol measure before treatment	Symptom measure after treatment	Results	Quality (points)
Rush, 1982	N = 14 Inclusionary criteria: major depressive disorder (Research Diagnostic Criteria), Hamilton Rating Scale for Depression Score ≥ 14 Exclusionary criteria: psychosis, bipolar disorder, concomitant major medical disorders, intake of barbiturates, meprobamate, reserpine, phenytoin, methyldopa, or glucocorticoids	Outpatient Non-randomised trial Cognitive therapy	Blood, dexamethasone administration at 11.30 pm (1 mg or 2 mg), subsequent measure at 4 pm	Responders: Beck Depression Inventory score ≤ 9	Five out of five non-suppressors (> 4 µg/dl) were non-responders, whereas eight out of nine suppressors were responders	7
Robbins, 1989	N = 38, mean age 15.6 (range:13-17) Inclusionary criteria: major depressive disorder (DSM-III), significantly incapacitated by their symptoms, eligible for dexamethasone suppression test Exclusionary criteria: significant medical illness, intake of psychotropic medication within past two weeks before dexamethasone suppression test	Inpatient Non-randomised trial Psychological therapy for at least six weeks, consisting of psychodynamically oriented interpersonal individual psychological therapy (three times per week), family therapy (once per week),	Blood, dexamethasone administration at 11 pm (1 mg), subsequent measures at 8 am, 4 pm, 11 pm	Responders: Schedules for Affective Disorders and Schizophrenia items on depression and anhedonia of < 3	All seven non-suppressors (> 5 µg/dl) were non-responders, whereas 18 out of 31 suppressors were responders	11

		group therapy (twice per week), and active cognitive-behavioural therapeutic milieu				
McKnight, 1992	N = 22 (22f) Inclusionary criteria: female, age ≥ 18 years, major depressive disorder (DSM-III), Depression Scale of Minnesota Multiphasic Personality Inventory score ≥ 29, Beck Depression Inventory score ≥ 20, Depression Adjective Checklist ≥ 18, Personal Beliefs Inventory score ≥ 3, willing to pay for blood tests, eligible for dexamethasone suppression test Exclusionary criteria: any other axis I disorder, suicidality, antidepressant or tranquilising medication within past two weeks, under care for the treatment of depression and missing statement from physician allowing discontinuation of treatment	Outpatient Randomised trial Weekly one-hour sessions of cognitive therapy for eight weeks (vs. treatment with tricyclic antidepressants)	Blood, dexamethasone administration at 11.30 pm (1 mg), subsequent measure at 4 pm	Beck Depression Inventory Depression Adjective Checklist Depression Scale of Minnesota Multiphasic Personality Inventory	The ten non-suppressors (≥ 5 µg/dl) had higher scores on all symptom measures when compared to the twelve suppressors (adjusted for pre-treatment symptom scores)	12
Thase, 1993	N = 22 Inclusion: predominant major depressive disorder (DSM-III-R), Hamilton Rating Scale for Depression score > 14 Exclusion: ill health, alcohol and drug intake within past two weeks	Inpatient Non-randomised trial Daily sessions of cognitive-behavioural therapy for four weeks, mean of	Urine, three consecutive 24 h collections	Beck Depression Inventory Hamilton Rating Scale for Depression	Cortisol levels were positively associated with scores on both symptom measures (post-treatment scores were highly correlated with their change scores: r = .92 and .96, respectively)	11

		12.9 sessions				
Thase, 1996	N = 29 (13f, 16m), mean age 32.7 (range: 18-54) Inclusionary criteria: age 18-70, major depressive disorder (DSM-III-R), index episode < 2 years duration, Hamilton Rating Scale for Depression score ≥ 15 Exclusionary criteria: history of alcoholism or drug abuse within past six months, history of manic, hypomanic, or psychotic episodes, mental retardation, history of comorbidity with any other axis I disorder, antisocial or borderline personality disorder, unstable medical condition that may cause depression or affect dexamethasone suppression test, unstable medication that may cause depression or affect dexamethasone suppression test, electroconvulsive therapy within past six months, past non-response to cognitive-behavioural therapy, continuation of pharmacotherapy	Inpatient Non-randomised trial Daily sessions of cognitive-behavioural therapy for four weeks, mean of 12.4 sessions	Urine, three consecutive 24 h collections Blood, dexamethasone administration at 11 pm (1 mg), subsequent measures at 8 am, 4 pm, 11 pm	Beck Depression Inventory Hamilton Rating Scale for Depression	Urinary free cortisol levels were negatively associated with change in both symptom measures Mean post-dexamethasone plasma cortisol levels were not associated with change in either symptom measure	10
Kundermann, 2009	N = 18 (7f, 11m), mean age 36.8 (SEM = 1.9) Inclusionary criteria: major depressive disorder (DSM-IV) Exclusionary criteria: comorbidity	Inpatient Randomised trial Daily sessions of cognitive-behavioural	Blood, +30, +45, +60 min after venepuncture, and +30, +45, +60, +90, +150 min after clomipramine administration	Responders: Hamilton Rating Scale for Depression reduction of ≥ 50%	Baseline cortisol levels (+60 min) did not differ between the nine non-responders and the nine responders (adjusted for age) Post-clomipramine cortisol output did not differ between the nine non-responders and the nine	12

	with any axis I or axis II disorder, suicidal tendencies, change of diagnosis during treatment, endocrine disorders, pregnancy or shift work within past three months, trans-meridian travel within past month, medication within past six days	therapy (with/without sleep deprivation) for three weeks			responders (adjusted for age)	
Gunlicks-Stoessel, 2013	N = 15 (13f, 2m), mean age 15.2 Inclusionary criteria: age 12-17, major depressive disorder, dysthymic disorder, depressive disorder NOS, or adjustment disorder with depressed mood (DSM-IV), Children's Depression Rating Scale revised score ≥ 36, Beck Depression Inventory II score ≥ 14, Children's Global Assessment Scale score ≤ 65, Conflict Behavior Questionnaire score ≥ 65 Exclusionary criteria: substance abuse, bipolar disorder, thought disorder, eating disorder, conduct disorder, mental retardation, current risk for suicide, medical illness likely to interfere with treatment, concurrent treatment for depression, concurrent treatment with psychotropic medication or unstable medication for attention deficit hyperactivity disorder within the past three months	Outpatient Randomised trial Weekly sessions of interpersonal therapy (with/without more involvement of parents) for 16 weeks	Saliva, baseline measure before discussion of an interpersonal conflict, subsequent measures +10, +20, +30 min	Children's Depression Rating Scale – revised version	Baseline cortisol levels were not associated with change in the symptom measure (alcohol abuse, medication, BMI, abuse, and time since awakening did not influence the analyses) Cortisol trajectories during the conflict were not associated with change in the symptom measure (alcohol abuse, medication, BMI, abuse, and time since awakening did not influence the analyses)	11
Holland, 2013	N = 54 (33f, 21m), mean age 70.2 (SD = 7.5)	Outpatient Non-randomised	Saliva, two consecutive days at awakening, 5 pm, 9	Beck Depression Inventory II	Diurnal cortisol output was not associated with change in any of the symptom measures	13

	Inclusionary criteria: older adults, major depressive disorder, dysthymia, or adjustment disorder with depressed mood, Center for Epidemiologic Studies Depression Scale score ≥ 16 Exclusionary criteria: dementia, active substance abuse, history of psychosis or mania, altering antidepressant use during study	trial Twelve one-hour sessions of cognitive-behavioural therapy for twelve to 16 weeks	pm	Center for Epidemiologic Studies Depression Scale Hamilton Rating Scale for Depression	Structural equation modelling yielded a negative association between cortisol output and flatter slopes with change in depression (adjusted for age, gender, ethnicity, years of education, marital status, antidepressant usage, estrogen hormone replacement therapy, general mental and physical health)

Table 2 Quality tool to assess risk bias in studies investigating the relationship between pre-treatment cortisol levels and psychological therapy response in patients with depressive disorders (modified from Tak et al., 2011)

1) Has the depressive disorder been reliably assessed and validated?	According to ICD-10, DSM-IV, or DSM-5 by a trained clinician (2) Not according to ICD-10, DSM-IV, or DSM-5 or assessor not clearly established (1) Self-report or not clearly stated (0)
2) Is the psychological treatment sufficiently described?	Both treatment duration and session frequency are reported (2) Only treatment duration or session frequency is reported (1) No information about treatment duration or session frequency are given (0)
3) Are the patients defined with in- and exclusion criteria?	Medication use, comorbidity with medical diseases, comorbidity with other mental disorders, 3 stated (2) Medication use, comorbidity with medical diseases, comorbidity with other mental disorders, 1-2 stated (1) None stated or not clearly stated (0)
4) Are disorder characteristics presented (duration and severity of major depressive episode)?	Duration and severity of disorder are stated (2) Only duration or only severity is stated (1) None stated (0)
5) Have the treating clinician and the person assessing treatment response been blind regarding pre-treatment cortisol levels?	Yes (2) Not clearly stated (0)
6) Are methods for measuring cortisol clearly stated?	Time of day, behaviour shortly prior to assessment, storage conditions, type of assay perfomed, repeated measurements, assessing compliance, 5-6 stated (2) Time of day, behaviour shortly prior to assessment, storage conditions, type of assay perfomed, repeated measurements, assessing compliance, 3-4 stated (1) Time of day, behaviour shortly prior to assessment, storage conditions, type of assay perfomed, repeated measurements, assessing compliance, 1-2 or none stated (0)
7) Are the relevant statistics clearly described and presented?	Both correlation coefficient and sample size available, frequency table available, or mean value and standard deviation available (2) Only sample size available or only mean value available (1) Relevant statistics not clearly stated (0)

8) Are potential confounders assessed?[a]	Age, gender, body mass index, smoking, pre-treatment severity of depression, medication, physical exercise, 5-7 stated (2) Age, gender, body mass index, smoking, pre-treatment severity of depression, medication, physical exercise, 3-4 stated (1) Age, gender, body mass index, smoking, pre-treatment severity of depression, medication, physical exercise, 1-2 or none stated (0)
9) Are the analyses adjusted for potential confounders?[b]	Age, gender, body mass index, smoking, pre-treatment severity of depression, medication, physical exercise, 5-7 stated (2) Age, gender, body mass index, smoking, pre-treatment severity of depression, medication, physical exercise, 3-4 stated (1) Age, gender, body mass index, smoking, pre-treatment severity of depression, medication, physical exercise, 1-2 or none stated (0)

[a]In case of exclusion at item 3, consider confounder as assessed

[b]In case of exclusion at item 3 or no significant impact on statistical analyses, consider confounder as adjusted for